Engineering novel paracetamol crystals for improved tabelting by direct compression for oral drug delivery

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INTRODUCTION

Paracetamol (PA, acetaminophen) is a popular analgesic. Currently, more than 90 products containing PA are available over the counter in the UK and are available in different dosage forms. The poor compression behaviour of PA powders is due to reduced plastic deformation during compression, resulting in the formation of soft tablets with a high capping tendency (1). Therefore, the aim of this work was to produce PA monoclinic crystals with improved compaction properties and dissolution rates using generally recognized as safe (GRAS) additives, i.e., polyvinyl alcohol (PVA), Avicel PH 102, Brij 58, methylcellulose (MC) and polyethylene glycols (PEG 1500, PEG 6000 and PEG 8000). The effect of the concentration of additives on the physicomechanical properties of crystallized paracetamol (Cry–PA) was also investigated.

METHODS

PA was dissolved in ethanol (40 °C, 30%, *w/v*). Twenty mL of this solution was then separately added to 50 mL of distilled water containing various additives (Avicel, Brij 58, MC, PEG or PVA) at different concentrations, i.e., 0.1%, 0.5% and 1% (*w/w*) for Brij 58, MC, PEG and PVA, and 2% (*w/w*) for Avicel. The precipitated crystals were recovered by vacuum filtration, dried (at 60 °C for 12 *h*) and stored in glass vials until required. PAs were characterized in terms of size (laser diffraction), morphology (scanning electron microscopy, SEM), solid-state (differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FT-IR)), true density (Ultrapycnometer 1,000) and flowability (Carr's index, CI). PAs were sieved to collect 90–125 µm particles and compressed using a single punch tableting machine (Enerpac MTCM–I, Globe Pharma, USA) fitted with 6 mm diameter flat–faced punches at 49, 98 and 147 MPa. Tablet crushing strength was determined (Dr Schleuniger Pharmatron, 8M, Switzerland). The dissolution profiles of sieved PA powders were evaluated using a USP dissolution apparatus no. 1 (Erweka DT700, Germany).

RESULTS AND DISCUSSION

Morphology

Following the crystallization of PA from ethanol in absence of any additives, PA crystals transformed from elongated habit (Figure 1*a*) to polyhedral-angular habit (Figure 1*b*).

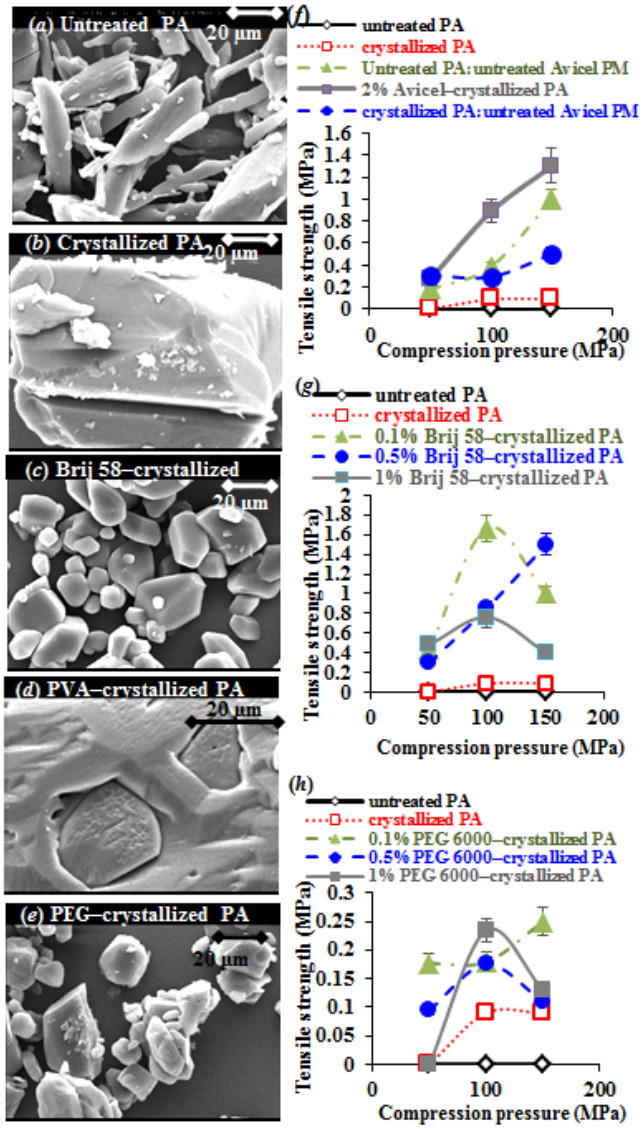

Figure 1. SEMs of untreated PA (a), Cry–PA (no additive) (b), Cry–PA in the presence of 0.1% (*w/w*) of Brij 58 (c), PVA (d), PEG 8000 (e), tensile strength of tablets comprised of untreated PA, Cry–PA (no additive), untreated Avicel:untreated PA physical mix, 2% (*w/w*) Avicel–Cry–PA and untreated Avicel:Cry–PA physical mix (*f*), Brij 58–Cry–PA (*g*) and PEG 6000–Cry–PA (*h*).

Additionally, the crystal size of untreated PA increased from a mean diameter (MD) of 148.3±10.8 µm to

197.8±8.4 µm. The crystal habit of PA crystallized in the presence of Brij 58 (Figure 1*c*) and PEG (Figure 1*e*) was subrounded-subangular whereas PA crystallized in the presence of PVA (Figure 3*d*) exhibited a polyhedral deformed habit. During crystallization, the additive could be adsorbed on the surfaces of the newly growing crystals, potentially competing for a site during the layer-by-layer crystal growth process, and thus could disrupt the intermolecular interactions between growth layers, leading to the formation of a crystal of a different habit.

Solid-state

Untreated and Cry–PAs produced comparable DSC scans as suggested by the presence of one endothermic transition at 170.9±1.1 ºC (melting onset = 169.2±0.3 ºC) (Figures not shown), corresponding to the melting of the stable form *I* (2). All the FT-IR bands representing the functional groups in the untreated PA were present in Cry–PAs with no shift (Figures not shown). This indicated that Cry–PAs did not undergo structural conversions compared to untreated monoclinic PA. This is considered advantageous because it allows the direct comparative evaluation of the PA products.

Density and flowability

True density of Cry–PA crystals was ≥ true density of untreated PA (1.27±0.02 – 1.60±0.01 g/cm^3 versus 1.26±0.02 g/cm^3). Cry–PA (no additives) demonstrated a considerably higher tap density than untreated PA (0.90±0.03 *versus* 0.53±0.01 g/cm^3). This could be due to the pronounced internal friction (i.e., additional void space) between untreated PA crystals due to their elongated habit (Figure 1*a*). All Cry–PA powders demonstrated improved flowability (CI: 10.1±2.4 – 43.1±2.7% *versus* 50.1±1.1%) compared to the untreated PA indicating their less cohesive behaviour. The better flowability of Cry–PA powders in comparison to untreated PA would be advantageous in achieving uniform tablet weight and hence acceptable drug content uniformity.

Compression and compaction

The Cry–PA (no additive) showed a slight improvement in compactibility in comparison to untreated PA (Figure 1*f*). Further improvement in tablet mechanical strength was observed when untreated PA was formulated with Avicel (Figure 1*f*). In comparison to both untreated PA and Cry–PA without additive, a significant improved hardness was observed for PA crystallized in the presence of Brij 58 (Figure 1*g*) and PEG 6000 (Figure 1*h*) at all compaction pressures; and to a lesser extent for PAs crystallized in the presence PEG 8000, PEG 1500, MC and PVA (Figures not shown). Such improvement in compactibility could be due to the polyhedral-angular habit of the latter PA crystals, which could lead to increased interparticle contact points and thus increased degree of densification during compression.

Dissolution

Among PA formulations investigated, 1% Brij 58–Cry–PA demonstrated the fastest dissolution pattern as reflected by the highest dissolution efficiency (DE_{60min} of 96.7±0.9%) and the shortest mean dissolution time (MDT of 2.0±1.0 min), whereas untreated PA crystals demonstrated the shortest dissolution pattern as reflected by the lowest DE_{60min} (90.1±0.2%) and the longest MDT (5.9±1.3% min) among PAs investigated (Figure 2). The relatively higher cohesive forces with untreated PA powder as indicated by CI (50.1 ± 1.1%) could potentially reduce the effective surface area for dissolution and thus may reduce bioavailability for untreated PA. Alternatively, the presence of hydrophilic additives could decrease the resistance to the effective diffusion of the solubilized PA in the case of Cry–PAs.

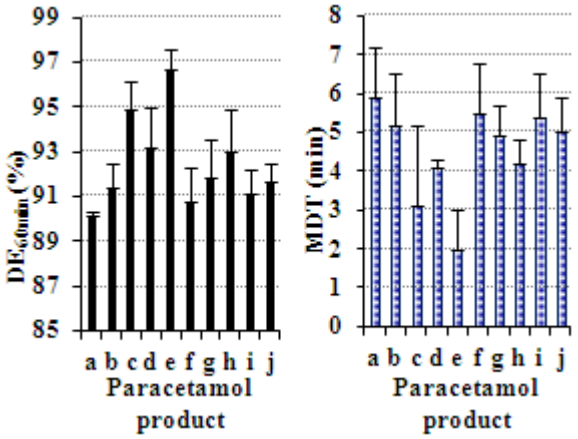

Figure 2. DE and MDT of untreated PA powder (*a*) and ethanol Cry–PA powders in the presence of different additives, i.e., Avicel (*b*), Brij 58 (0.1% (*c*), 0.5% (*d*), 1% w/w (*e*)), methylcellulose (MC, *f*) and polyethylene glycol (PEG 6000, 0.1% *w/w* (*g*) and PEG 8000 0.1% (*h*), 0.5% (*i*) and 1% (*j*)).

CONCLUSION

Engineered paracetamols with improved micromeritic, mechanical and dissolution properties were prepared by antisolvent crystallization technique in the presence of various hydrophilic additives. The polyhedral crystallized form of paracetamol produced stronger tablets than elongated untreated crystals of paracetamol. paracetamols crystallized in the presence of Avicel, Brij 58 and PEG 6000 were more advantageous and showed the best compactibility when compared to other paracetamols.

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